

REMARKS

Claims 19 to 34 are in the application. Claims 19 and 27 have been amended. Applicants reserve their right to file divisional or continuation applications on cancelled or deleted subject matter. No new matter is believed added.

Applicants respectfully request the grant of an interview with the Examiner if the claims are not found in condition for allowance upon review of this response. The Examiner is requested to contact the undersigned at the number indicated below to set up such a meeting, if necessary.

Rejection under 35 USC § 102(b)

Claims 19 to 21, 25 to 29, 33 and 34 are rejected under 35 USC §102 (b) as being anticipated by Folino et al. (Folino, J. Nutr. 125: 1521-28, 1995).

Claims 19 to 22, and 27 to 30 are rejected under 35 USC §102(b) as being anticipated by Shah (Shah et al., US Patent 4,671,823)

Claims 19 to 34 are rejected under 35 USC §102(e) as being anticipated by Dressman et al. (US Patent 5,789,393). Applicants respectfully traverse these rejections.

The Examiner appears to be maintaining a rejection of anticipation for a novel method of administration on the basis of a disclosure of a similar or same composition. This does not produce an anticipatory reference in any of the above rejections. Applicant's claims are directed to a novel method of use, i.e. reduction of the incidence of colorectal cancer or of breast cancer in a human, not a compound or composition.

The Folino et al. reference, the Shah et al. patent, and Dressman et al. all fail to disclose the **claimed** usage of a composition consisting essentially of methylcellulose, alone or in combination with wheat bran, and therefore all three fail to render the claims anticipated. Applicants are not claiming a compound or a composition such as described by the Folino et al. reference, the Shah et al. patent, or the Dressman et al. patent, but a *novel usage* of such a composition as described therein.

The Shah et al. patent is but one of several suitable compositions comprising methylcellulose which could be used in the methods of the present invention. Dressman et al. is directed to high viscosity grade cellulose ether compositions (see column 9, lines 27 to 58). The approved products of methylcellulose on the US market are generally in the range of about 4000 centipoise. This is significantly below the high molecular weight methylcellulose and hydroxypropylmethylcellulose contemplated for use by Dressman et al. for lipid lowering. The use contemplated by Dressman et al. is also a different method than that contemplated by Applicants

herein, i.e., reduction in the incidence of colorectal cancer. The use of an old composition in a novel method does not render the new method anticipated.

To anticipate a claim, a single source must contain all of the elements of the claim, see *Hybritech Inc. v Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir., 1986). Consequently, neither the Folino et al. reference, nor the Shah et al. patent, nor the Dressman et al. patents contain **all** the required elements of Applicants claims herein.

Consequently, withdrawal of the rejections to the claims under 35 USC §102(b) is respectfully requested.

Rejection under 35 USC §103

Claims 19 to 21, 25 to 29, 33 and 34 are rejected under 35 USC §103(a) as being unpatentable over Folino et al. , in view of Cohen et al. (J Nat'l Cancer Inst., 88(13): 899-907, 1996).

Claims 19 to 21, and 27 to 29 are rejected under 35 USC §103(a) as being unpatentable over Folino et al., in view of Cohen et al. or Alabaster et al. (Alabaster, O et al., Cancer Letters, 75: 53-58, 1993).

Claims 19 to 23, 25 to 31, 33 and 34 are rejected under 35 USC §103(a) as being anticipated by Dressman et al., in view of Durlach (US Patent 4,232,054). Applicants respectfully traverse all of these rejections.

It is believed that the Examiner in the last rejection (newly added) to Dressman et al. in view of Durlach mean to say that the claims ... are rejected under 35 USC §103 as being unpatentable, not anticipated by Dressman et al., etc. Clarification of this rejection is requested if this is not correct so that Applicants may have the opportunity to respond accordingly.

The Examiner comments that the "claimed methods read on methods comprising the administration of methylcellulose to a human". Applicants do not disagree that one part of the claimed methods require administration of methylcellulose, alone or with wheat bran, to a human. However, this argument misses the main purpose of administering the methylcellulose, i.e. to achieve a reduction in the incidence of colorectal cancer or breast cancer in the human who is taking the methylcellulose. In order to better clarify this point, Applicants have moved the purpose of the administration from the preamble to the body of the claim.

The present invention is directed to use of a water soluble, non-fermentable cellulose derivative, methylcellulose, alone or in combination with a second fiber,

such as an insoluble fiber like wheat bran, or a soluble (but fermentable, fiber like psyllium), for the reduction of either colon cancer and/or breast cancer.

As Folino et al. is the primary reference in both of the two 35 USC §103 rejections, Folino et al. will be discussed in greater detail herein. Folino et al. teaches that epithelial proliferation, using a metaphase arrest method, is dependent upon the type of fiber chosen for use, with methylcellulose > coarse wheat bran > fine wheat bran = rice bran > no fiber.

The end result of the teachings of the Folino et al. reference is *epithelial proliferation*. The epithelial proliferation looked for is that of the rapidly dividing tissues or cells in the colon. This marker, or result, in the Folino et al. reference is not the same as looking for cancerous, or neoplastic cell differentiation. The Folino et al. method does not measure tumors, or tumor growth in contrast to that described in the specification herein.

The Folino et al. reference concludes that methylcellulose will increase the rate of cell division, have a high stool output, is acidic and will not ferment, and therefore no SCFA's will be present, and that there will be no decrease in the pH.

This result can be seen in the Abstract of the Folino et al. article, wherein the effect on stool output is also described as ranking identically to that above. While this certainly confirms the use of methylcellulose as a laxative, it does not meet the preferred criteria of Folino et al. for the other desired aspects. The following sentence in the abstract then discusses pH effects with "most to least" and methylcellulose is at the end, showing equal to a placebo or no fiber at all.

The Folino et al. reference concludes that different fibers have different effects on the fecal environment, and are therefore hard to predict what the protective effect would be. Applicants claims are not directed to a general group of all types of dietary fibers, but a specific group of non-fermentable water soluble cellulose fibers, in particular methylcellulose (claim 19 and 27). Applicants in contrast to the data shown in the Folino et al. reference, also demonstrate positive data on reducing the incidence of tumors (the claimed result).

The Folino et al. reference teaches that you can feed fiber to rats. It does not teach that these fibers have a protective effect against colon cancer, alone or with wheat bran, as claimed in claim 19. It does not demonstrate a benefit, just that different conditions and variables could generate or give rise to differing risks.

The present invention looks at a measure of colon carcinogenesis, a precursor to tumors. The two examples described in the specification, pages 3, lines 30 to end, page 4 to 5 in their entirety, and page 6, lines 1 to 24) clearly demonstrate that use of a water soluble, non-fermentable cellulose ether, i.e. methylcellulose, is effective to

reduce the risk of colon cancer, using the aberrant crypt foci (see Example 1) method. This method it should be noted, is an art - recognized method for measuring cancerous and precancerous conditions, in contrast to that described in the Folino et al. article.

Folino et al. does not measure a form of cancer, or even a precancerous condition. Folino et al. does not teach a method from which one can reach Applicants conclusion, nor does Folino et al. show a reduction of tumors. From the Folino et al. article you find 1 positive (or pro feature) for methylcellulose and 3 negative (or con features) described therein.

Prior to the cited Alabaster studies herein, it was shown that psyllium was not deemed protective against colon cancer. The first Alabaster et al. reference (Alabaster I – Cancer Letters 75:53-58 , 1993) teach that wheat bran (and insoluble fiber) has a protective role, and that wheat bran in combination with psyllium is better than either alone. Alabaster II (Mutation Research 350:185-197, 1996), using the same type of experimental models, and the aberrant crypt foci method (as used by the present invention herein), also concludes that wheat bran alone, or in combination with psyllium and other nutrients, (see abstract) was effective to reduce aberrant crypt foci and colon tumors in their model.

The Folino et al. reference shows that psyllium will decrease the pH, increase the level of butyrates (SCFA), increase output and as for proliferation, increase it over no fiber at all (placebo). Therefore, this article states that there are 3 positive measures for psyllium, and maybe one negative. Looking at this same article for methylcellulose, however, the skilled artisan is directed away from using methylcellulose over psyllium. Therefore, the skilled artisan would not be motivated to substitute an entirely different type of dietary fiber for psyllium.

Folino et al. also teaches more importantly that the dietary fibers are not predictive, thereby teaching away from Applicants claimed invention. Folino et al. does not teach that use of methylcellulose would have a protective effect on carcinogenesis. Therefore, there is no motivation, taken alone or when combined with other references which would direct the skilled artisan to the conclusion that methylcellulose would have a protective effect on colon cancer or breast cancer.

As previously noted, this deficiency is not remedied by the Cohen et al. reference which is also a study on wheat bran and psyllium, but not water soluble non-fermentable cellulose directives (as required by claims 19 and 27 herein). Similar to the Alabaster I and II studies, wheat bran is shown to be effective, and wheat bran in combination with psyllium is also effective to offer protection against breast cancer risk.

Cohen et al. does not teach nor suggest the use of water soluble non-fermentable cellulose derivatives. None of these references provide a basis to substitute or to include with wheat bran or psyllium a methylcellulose like product and expect to achieve Applicants claimed invention herein.

Dressman et al. as discussed above discloses high viscosity, high molecular weight cellulose ethers, and primarily hydroxypropylmethylcellulose. The approved products of methylcellulose products approved and made available to the public are in the range of about 4000 centipoise. This is significantly below the high molecular weight methylcellulose and hydroxypropylmethylcellulose contemplated for use by Dressman et al. for lipid lowering. The use contemplated by Dressman et al. for such high viscosity, high molecular weight cellulose ethers is a different method than that contemplated by Applicants herein, i.e., reduction in the incidence of colorectal cancer. Dressman et al. does not teach administration of such compositions for reduction of colorectal or breast cancer as noted by the Examiner.

The Examiner comments that the deficiency of Dressman et al. is remedied by the teaching of Durlach. However, Durlach does not disclose the claimed method of use herein. Durlach attempts to remedy the loss of calcium, magnesium etc. by the chelating action of various fibers, by adding to the diet, various metallic proteins, i.e. ca, mg, iron, zinc, etc. as contained in milk or egg protein, to the vegetable fibers, i.e. wheat bran. Durlach does not teach Applicants invention, and therefore when taken with Dressman et al. render Applicants claims unpatentable.

In light of these remarks and amendments, Applicants respectfully request reconsideration and withdrawal of the rejection to the claims under 35 USC §103 (a).

Rejection under 35 USC § 112, second paragraph

Claims 19 to 34 are rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as in invention. Applicants respectfully traverse this rejection.

Claim 19 has been amended to correct for lack of antecedent basis. Attention to this error by the Examiner is greatly appreciated.

The Examiner also comments that the two main claims, 19 and 27 are indefinite as to the "reduction in incidence of cancer", i.e. that the specification does not provide a definition. Applicants respectfully disagree that a specific number need be assigned to a decrease in the current incidence of a cancer. The Examples, such as Example 1, clearly demonstrates that by increasing the dietary fiber concentration

from 1 to 8% significantly reduced the number of tumors/ group as compared to the psyllium based control. The skilled artisan would readily recognize that there is a significant effect on the two groups as shown in the Alabaster study.

The phrase in "humans in need" is also not believed to be indefinite as the application clearly indicates (page 4, lines 23-25) that the human population eating a western diet is clearly an at risk population.

In view of these comments and amendments, reconsideration and withdrawal of the rejection to the claims under 35 USC §112, second paragraph is respectfully requested.

CONCLUSION

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



Dara L. Dinner
Attorney for Applicants
Registration No. 33,680

SMITHKLINE BEECHAM CORP.
Corp. Intellectual Property-U.S. (UW2220)
P.O. Box 1539
King of Prussia, PA 19406
(610) 270-5017 - Telephone
(610) 270-5090 - Facsimile

750870a2.doc